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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,384	12/20/2000	Martin M. Bednar	P1729C1	9289

9157 7590 09/30/2002

GENENTECH, INC.
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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/811384	Applicant(s) BERMAN
	Examiner GAMBEL	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on _____ is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. If applicant desires priority under 35 U.S.C. 119(e) or 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of non-provisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

2. It is not readily apparent that the instant claimed limitations receive priority back to the earliest priority date of 1/23/96. Applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

3. Applicant's application is in compliance with the Sequence Rules.

4. Formal drawings have been submitted which comply with 37 CFR 1.84.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

6.The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11-12: It is apparent that the H52 antibody is required to practice the claimed invention (claims 11-12). As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

It is noted that if the claimed amino acid sequences of the heavy and light chain of the humanized H52 antibody are disclosed on pages 12-13 of the instant specification. The sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin. Given the same claim limitations in priority application USSN 08/7888,800, now U.S. Patent 5,914,112 (1449, #8). The claims are in compliance with the requirements under 35 USC 112, first paragraph, for the deposit of biological materials.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-10 and 12-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mori et al. (Stroke 23: 712-718, 1992; 1449, #69) OR Clark et al. (Stroke 22: 877-883, 1991; 1449, #45) OR Bednar et al. (Neurol. Res. 18: 171-175, 1996; #34) OR Lindsberg et al. (J. Neurosurg. 82: 269-277, 1995; #66) in view of art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients as well as the administration of tPA and certain modes of administration to meet the needs of the patients as acknowledged on pages 7-20 and 25-26 of the instant specification.

Mori et al. teach inhibiting focal cerebral ischemia in baboons with the anti-CD18 antibody IB4 (see entire document).

Clark et al. teach reducing central nervous systemic ischemic injury in rabbits with anti-CD18 antibodies (see entire document).

Bednar et al. teach reducing intracranial pressure following thromboembolic stroke in the rabbit with the anti-CD18 antibody IB4 (see entire document).

Lindsberg et al. teach the ability of the anti-CD18 antibody given after the onset of reperfusion to treat a spinal-cord ischemia-reperfusion injury in rabbits (see entire document).

Mori et al., Clark et al., Bednar et al. and Lindsberg et al. differ from the instant methods by not employing antibody fragments or humanized antibodies or treating human patients, however such antibody modifications were standard procedures in increasing therapeutic efficacy and in treating human patients at the time the invention was made.

Mori et al., Clark et al., Bednar et al. and Lindsberg et al. differ from the instant methods by not teaching the particular claimed time frames of 45 minutes to 5 hours and 15 minutes to about 20 hours, however the references do teach treating within these time frames. In addition, such time frames as well as providing bolus/continuous infusion would have obvious to the ordinary artisan at the time the invention was made in providing sufficient anti-CD18 antibody depending on the need of the patient.

Also, Mori et al., Clark et al., Bednar et al. and Lindsberg et al. differ from the instant methods by not teaching the well known use of tPA to increase cerebral blood flow and/or reduce infarct size in focal ischemic stroke, however the use of tPA had been well known and practiced by the ordinary artisan in the treatment of focal ischemic attack at the time the invention was made.

Pages 7-20 and 25-26 of the instant specification acknowledges the well known use and practice of administering chimeric and humanized antibodies and antibody fragments in human therapeutic regimens at the time the invention was made, given the homogeneity and decreased immunogenicity of these recombinant antigen binding molecules. In addition, the instant specification acknowledges the well known use of tPA in the treatment of focal ischemic stroke at the time the invention was made and that dosages and modes of administration were known and practiced by the ordinary artisan at the time the invention was made to meed the needs of the patient in such therapeutic regimens.

One of ordinary skill in the art at the time the invention was made would have been motivated to select anti-CD18 antibodies in combination with tPA to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size by delaying the administration of such treatment after the onset of focal ischemic stroke in order to meet the needs of certain stroke patients at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claims 11-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Mori et al. (Stroke, 1992) OR Clark et al. (Stroke, 1991) OR Bednar et al. (Neurol. Res., 1996) OR Lindsberg et al. (J. Neurosurg, 1995) in view of art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients as applied to claims 1-10 and 13-18 above and in further view of Hildreth et al. (Mol. Immunol. 26: 1155-1167, 1989; 1449, #56) OR Hildreth (WO 90/15076; 1449; #18).

Mori et al., Clark et al., Bednar et al. and Lindsberg et al., differ from the instant claims by not disclosing the H52 specificity.

Both Hildreth et al. references teach the H52 specificity. It is noted that the complete Hildreth (WO 9015076) document was not available to the examiner at this time, however it is clear that this reference teaches the use of the H52 antibody in various therapeutic modalities. Hildreth et al. (Mol. Immunol.)

Although the references are silent about the exact sequences of the H52 antibody, the recombinant techniques and computer analyses of CDR grafting known and well-practiced at the time the invention was made would have resulted in the same or very nearly the same structural and functional characteristics of the instant humanized H52 antibody and fragments thereof, since both the references and instant invention use the same techniques, the same antibody specificities and the same goals. There appears no evidence that the instant humanized H52 antibody would differ in an unexpected or distinct manner from that available to the ordinary artisan at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have been motivated to select various anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size, including the treatment of human ischemic stroke, including the instant H52 specificity as taught by Hildreth et al., to meet the needs of the patient at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,914,112 (1449, #8) in view of the administration of tPA and certain modes of administration to meet the needs of the patients as acknowledged on pages 7-20 and 25-26 of the instant specification. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to the same or nearly the same methods of treating focal ischemic stroke with CD18-specific antibodies, including the H52 antibody specificity. Although, the patented claims do not recited the well known use and practice of tPA and certain modes of administration per se, the instant claimed limitations of employing tPA and certain modes of administration were well and practiced by the ordinary artisan to meet the needs of the patients at the time the invention was made, as acknowledged on pages 7-20 and 25-26 of the instant specification.

Claims 1-18 are directed to an invention not patentably distinct from claims 1-18 of commonly assigned U.S. Patent No. 5,914,112 (1449, #8) in view of the administration of tPA and certain modes of administration to meet the needs of the patients as acknowledged on pages 7-20 and 25-26 of the instant specification for the reasons above.

Commonly assigned U.S. Patent No. 5,914,112, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, Ph.D.
Primary Examiner
Technology Center 1600
September 30, 2002

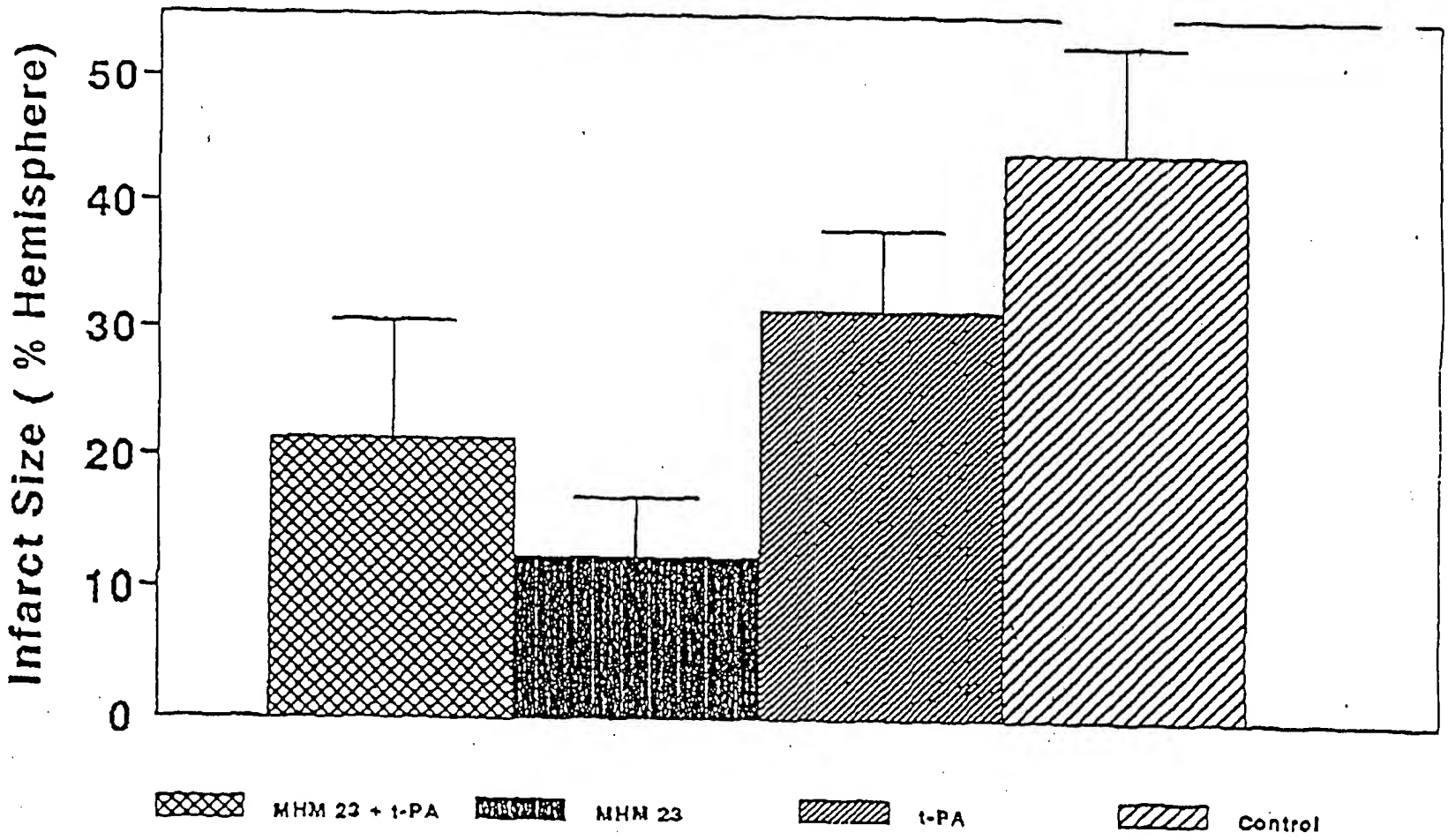

Figure 1

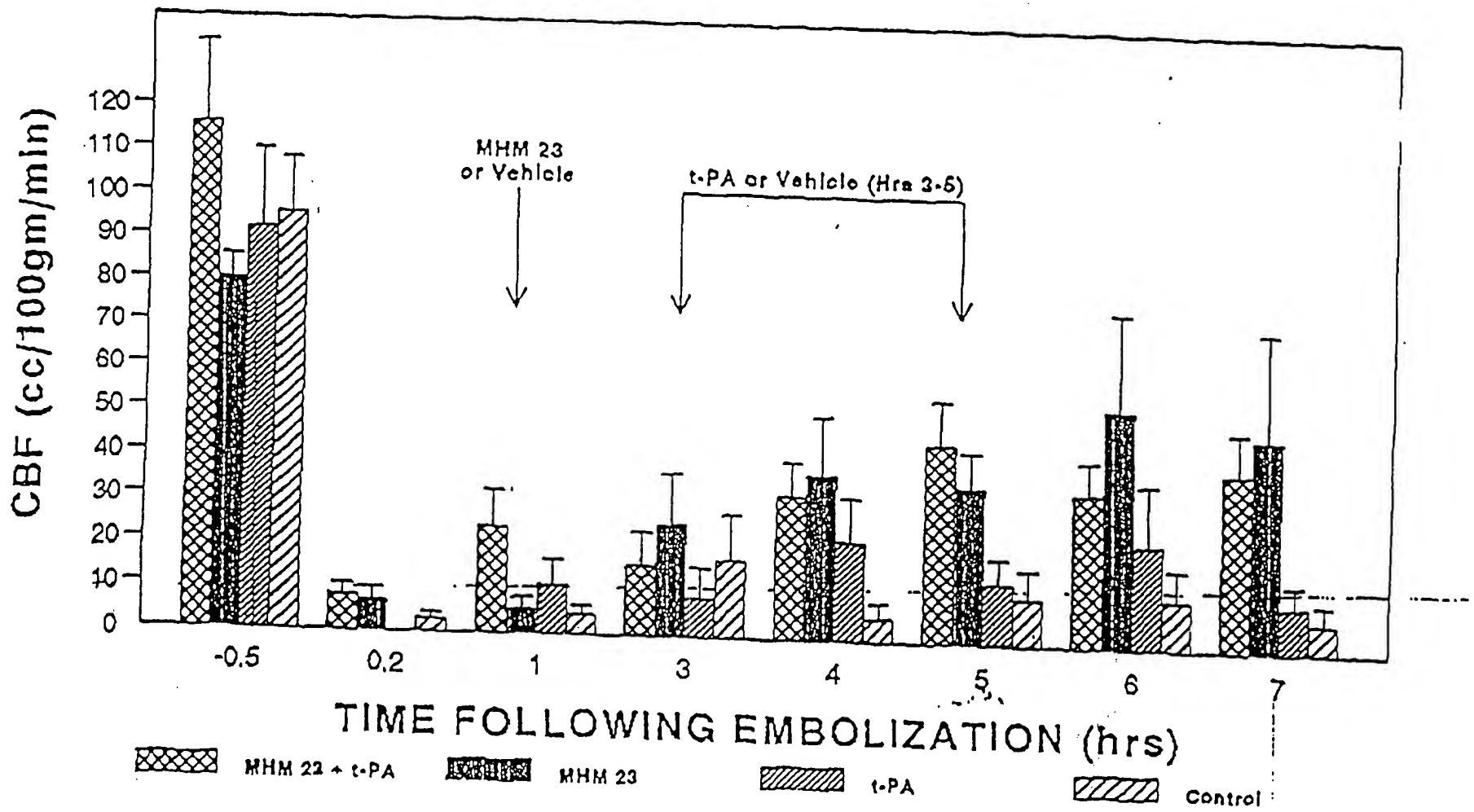

Figure 2

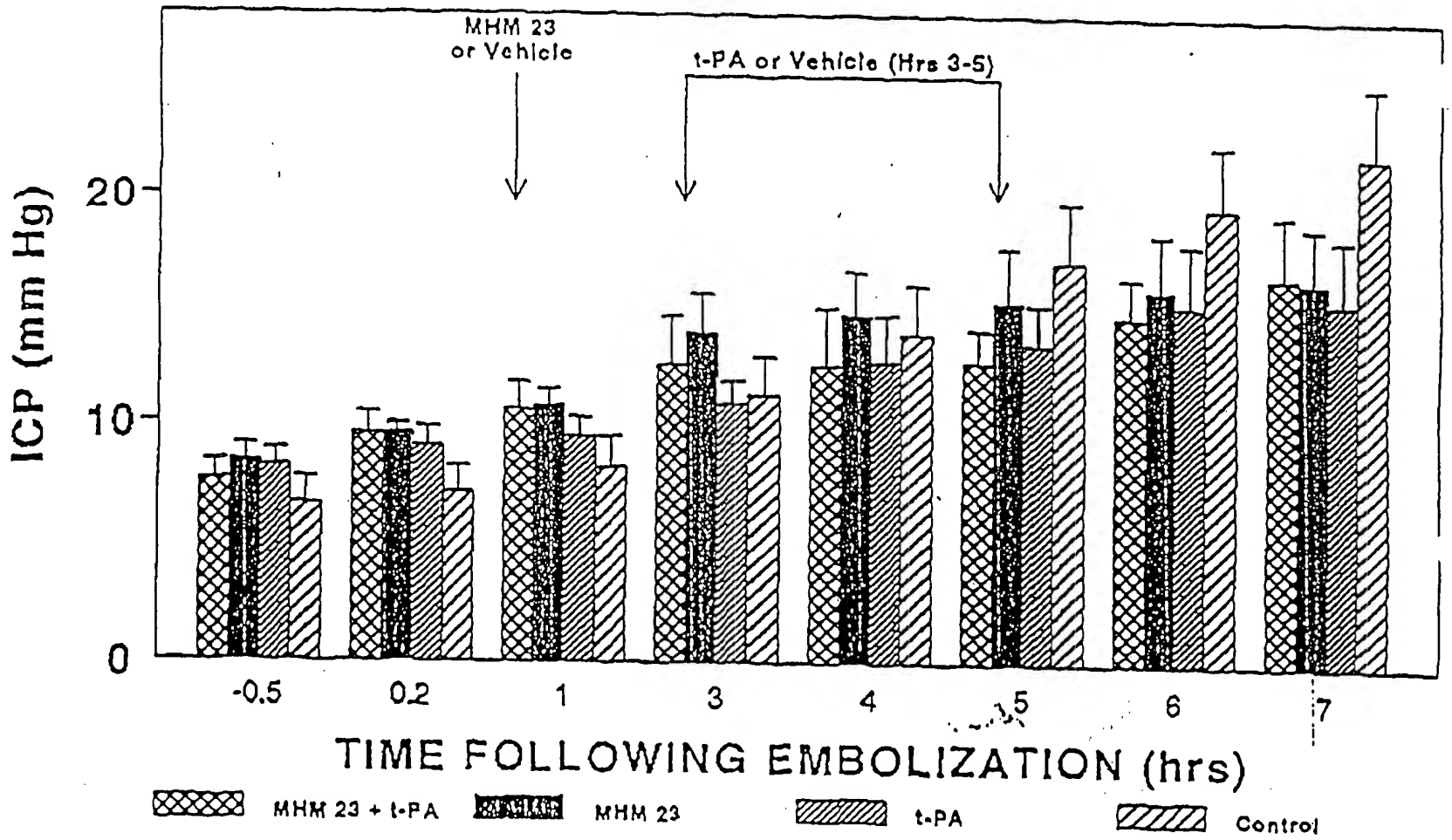

Figure 3

$hIgG_1$ Sequence of human IgG1 CH1 domain
$hIgG_2$ Sequence of human IgG2 CH1 domain
$hIgG_3$ Sequence of human IgG3 CH1 domain
$hIgG_4$ Sequence of human IgG4 CH1 domain
humκ Sequence of human kappa CL domain
humλ Sequence of human lambda CL domain

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==========================================================

          114                             128             139
           |                               |               |
hIgG1     A S T K G P S V F P L A P S S K S T S G G T A A L
hIgG2     A S T K G P S V F P L A P C S R S T S E S T A A L
hIgG3     A S T K G P S V F P L A P C S R S T S G G T A A L
hIgG4     A S T K G P S V F P L A P C S R S T S E S T A A L

          108                             122             131
           |                               |               |
humκ       R T V A A P S V F I F P P S D E Q L K S G T A S V
humλ       Q P K A A P S V T L F P P S S E E L Q A N K A T L

           ----------------------------------------------

Fabv1b    A S T K G P S V F P L A P S P K N S SMISN T P A L
of interest                          P K N S SMISN T P
                                     ____________________
most important                                *** *

hIgG1     G C L V K D Y F P E P V T V S W N S G A L T S
hIgG2     G C L V K D Y F P E P V T V S W N S G A L T S
hIgG3     G C L V K D Y F P E P V T V S W N S G A L T S
hIgG4     G C L V K D Y F P E P V T V S W N S G A L T S

humκ       V C L L N N F Y P R E A K V Q W K V D N A L Q
humλ      V C L I S D F Y P G A V T V A W K A D S S P V

           ------------------------------------------

Fabv1b    G C L V K D Y F P E P V T V S W N S G A L T S

hIgG1     G V H T F P A V L Q S S G - - - L Y S L S S V
hIgG2     G V H T F P A V L Q S S G - - - L Y S L S S V
```

Figure 4A

```
hIgG3       G V H T F P A V L Q S S G - - - L Y S L S S V
hIgG4       G V H T F P A V L Q S S G - - - L Y S L S S V
humκ         S G N S Q E S V T E Q D S K D S T Y S L S S T
humλ        K A G V E T T T P S K Q S N N - K Y A A S S Y
            ----------------------------------------
Fabv1b      G V H T F P A V L Q S S G - - - L Y S L S S V

                193                 200 203
                 |                   |   |
hIgG1       V T V P S S S L G T - Q T Y I C N V N H K P S
hIgG2       V T V P S S N F G T - Q T Y T C N V D H K P S
hIgG3       V T V P S S S L G T - Q T Y T C N V N H K P S
hIgG4       V T V P S S S L G T - K T Y T C N V D H K P S
                      181                 190
                       |                   |
humκ         L T L S K A D Y E K H K V Y A C E V T H Q G L
humλ        L S L T P E Q W K S H R S Y S C Q V T H E G S
            ----------------------------------------
Fabv1b      V T V P H Q S L G T - Q T Y I C N V N H K P S
of interest       H Q N L S D G K
                  ---------------
most important    * * *     *   *


hIgG1       N T K V D K R V - - -
hIgG2       N T K V D K T V - - -
hIgG3       N T K V D K R V - - -
hIgG4       N T K V D K R V - - -

humκ        S S P V T K S F N R G E C
humλ         T V E K T V A P T E C S
            ------------------------
Fabv1b      N T K V D K R V - - -
```

Figure 4B

DETAILED ACTION

1. If applicant desires priority under 35 U.S.C. 119(e) or 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of non-provisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

In clarifying the priority date of the instant claims, applicant should note or address whether the art rejections are prior to the priority date of the instant claims and whether said art occurred more than one year prior to the priority date of 1/22/97 or to the putative priority date of 1/23/96.

2. Applicant's application is in compliance with the Sequence Rules.

3. Formal drawings have been submitted which comply with 37 CFR 1.84.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

It does not appear that a sequence listing has been provided for the light chain of the full length IgG2 huH52 as disclosed on page 13, lines 9-12 of the instant specification.

5.The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Claims :

It is apparent that the H52 antibody is required to practice the claimed invention (claims 11-12). As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

It is noted that if the claimed amino acid sequences of the heavy and light chain of the humanized H52 antibody are disclosed on pages 12-13 of the instant specification. The sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin. However, if the amino acid sequences disclosed in the instant specification do not encompass the entire native H52 antibody, then applicant is required to deposit the H52 hybridoma to satisfy the deposit of biological materials under 112, first paragraph, as set forth above.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11.

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-2, 6-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Mori et al. (Stroke, 1992). Mori et al. teach inhibiting focal cerebral ischemia in baboons with the anti-CD18 antibody IB4 (see entire document). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods antibodies.

13. Claims 1-2, 6-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Clark et al. (Stroke, 1991). Clark et al. teach reducing central nervous systemic ischemic injury in rabbits with anti-CD18 antibodies (see entire document). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods antibodies.

14. Claims 1-2, 6-10 are rejected under 35 U.S.C. § 102(a) as being anticipated by Bednar et al. (Neurol. Res., 1996). Bednar et al. teach reducing intracranial pressure following thromboembolic stroke in the rabbit with the anti-CD18 antibody IB4 (see entire document). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods antibodies.

15. Claims 1-2, 6-10 are rejected under 35 U.S.C. § 102(a) as being anticipated by Bednar et al. (Neurol. Res., 1996). Bednar et al. teach reducing intracranial pressure following thromboembolic stroke in the

rabbit with the anti-CD18 antibody IB4 (see entire document). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced methods antibodies.

16. Claims 1-10 and 15-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Mori et al. (Stroke, 1992) OR Clark et al. (Stroke, 1991) OR Bednar et al. (Neurol. Res., 1996) OR Lindsberg et al. (J. Neurosurg, 1995) in view of art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients.

Mori et al. teach inhibiting focal cerebral ischemia in baboons with the anti-CD18 antibody IB4 (see entire document).

Clark et al. teach reducing central nervous systemic ischemic injury in rabbits with anti-CD18 antibodies (see entire document).

Bednar et al. teach reducing intracranial pressure following thromboembolic stroke in the rabbit with the anti-CD18 antibody IB4 (see entire document).

Lindsberg et al. teach the ability of the anti-CD18 antibody given after the onset of reperfusion to treat a spinal-cord ischemia-reperfusion injury in rabbits (see entire document).

Mori et al., Clark et al., Bednar et al., Lindsberg et al. differ from the instant methods by not employing antibody fragments or humanized antibodies or treating human patients, however such antibody modifications were standard procedures in increasing therapeutic efficacy and in treating human patients at the time the invention was made.

Mori et al., Clark et al., Bednar et al., Lindsberg et al. differ from the instant methods by not teaching the particular claimed time frames of 45 minutes to 5 hours and 15 minutes to about 20 hours, however the references do teach treating within these time frames. In addition, such time frames as well as providing bolus/continuous infusion would have obvious to the ordinary artisan at the time the invention was made in providing sufficient anti-CD18 antibody depending on the need of the patient.

Claims 15-17, drawn to articles or manufacture and kits would have been obvious at the time invention was made in providing anti-CD18 antibodies in a form including the instructions for its use intended for the treatment of ischemic stroke, as taught by the references above. It was well known convention in the art to place components in a kit for convenience and economy.

One of ordinary skill in the art at the time the invention was made would have been motivated to select anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole

was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 1-10 and 15-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Mori et al. (Stroke, 1992) OR Clark et al. (Stroke, 1991) OR Bednar et al. (Neurol. Res., 1996) OR Lindsberg et al. (J. Neurosurg, 1995) in view of art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients as applied to claims 1-10 and 15-17 above and in further evidence of Kim et al. (J. Neurological Sciences, 1995) as it applies to instant methods treating humans.

Kim et al. Provide evidence that CD11a and CD18 are unregulated in patient with ischemic stroke and transient ischemic attacks and that such adhesion molecules are involved in tissue injury in various cerebral vascular disorders including ischemic stroke (see entire document).

One of ordinary skill in the art at the time the invention was made would have been motivated to select anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size, including the treatment of human ischemic stroke. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Claims 11-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Mori et al. (Stroke, 1992) OR Clark et al. (Stroke, 1991) OR Bednar et al. (Neurol. Res., 1996) OR Lindsberg et al. (J. Neurosurg, 1995) in view of art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients as applied to claims 1-10 and 15-17 above and in further view of Hildreth et al. (Mol. Immunol., 1989) OR Hildreth (WO 9015076).

Mori et al., Clark et al., Bednar et al., Lindsberg et al., differ from the instant claims by not disclosing the H52 specificity.

Both Hildreth et al. references teach the H52 specificity. It is noted that the complete Hildreth (WO 9015076) document was not available to the examiner at this time, however it is clear that this reference teaches the use of the H52 antibody in various therapeutic modalities. Hildreth et al. (Mol. Immunol.)

Although the references are silent about the exact sequences of the H52 antibody, the recombinant techniques and computer analyses of CDR grafting known and well-practiced at the time the invention was made would have resulted in the same or very nearly the same structural and functional characteristics of the instant humanized H52 antibody and fragments thereof, since both the references and instant invention use the same techniques, the same antibody specificities and the same goals. There appears no evidence that the instant humanized H52 antibody would differ in an unexpected or distinct manner from that available to the ordinary artisan at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have been motivated to select various anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size, including the treatment of human ischemic stroke, includig the instant H52 specificity as taught by Hildreth et al.. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claim 13 is rejected under 35 U.S.C. § 103 as being unpatentable over Mori et al. (Stroke, 1992) OR Clark et al. (Stroke, 1991) OR Bednar et al. (Neurol. Res., 1996) OR Lindsberg et al. (J. Neurosurg, 1995) in view of art known methods at the time the invention was made to employ antibody fragments and humanized antibodies to increase therapeutic intervention including targeting human patients as applied to claims 1-10 and 15-17 above in view that the instant salvage receptor epitope would be derived from recombinant modeling of humanized antibodies OR in view of Presta et al. (WO 96/32478) if the instant salvage receptor epitopes are drawn to SEQ ID NOS. 8, 9, and 13-15 as salvage receptor binding epitopes.

Mori et al., Clark et al., Bednar et al., Lindsberg et al., differ from the instant claims by not disclosing salvage receptor binding epitopes.

Given the absence of clear structural limitations, the instant salvage receptor binding epitopes would read on modifications in deriving humanized antibodies including modifications to decrease immunogenicity and increase half-life via standard recombinant methods known and practiced at the time the invention was made.

Alternatively, Presta et al. teach salvage receptor epitopes to increase the half-life of antibodies, including those disclosed in the instant specification (though not claimed).

One of ordinary skill in the art at the time the invention was made would have been motivated to modify therapeutic antibodies to decrease immunogenicity and to increase half-life to increase their efficacy, including anti-CD18 antibodies to treat focal ischemic stroke to increase cerebral blood flow or reduce infarct size, including the treatment of human ischemic stroke. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. No claim is allowed.

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